CLAIMS

What is claimed is:

1. A method of inhibiting formation of neurofibrillary tangles in an individual, said method comprising: reducing formation of a carboxyl-terminal truncated form of apoE in a neuron in the individual.

2. The method of claim 1, comprising administering to the individual an agent that reduces a proteolytic activity of an enzyme that catalyzes the proteolytic degradation of apoE in a neuronal cell.

3. The method of claim 1, wherein the reduction in formation of carboxyl-terminal truncated apoE treats a disorder related to apoE in an individual.

4. The method of claim 3, wherein the disorder is selected from the group consisting of Alzheimer's disease, coronary artery disease, head trauma, and stroke.

5. The method of claim 3, wherein the apoE is apoE4.

6. The method of claim 5, wherein the carboxyl-terminal truncated form of apoE4 is apoE4 (Δ272-299).

7. A transgenic non-human animal comprising a transgene stably integrated into the genome of said animal, wherein said transgene comprises a nucleotide sequence encoding carboxyl-terminal truncated apoE operably linked to a promoter such that carboxyl-terminal truncated apoE-encoding sequences are expressed, and carboxyl-terminal truncated apoE protein is synthesized, in a neuron in said animal, and wherein, as a result of said synthesis of said carboxyl-terminal truncated apoE protein, said transgenic animal develops symptoms of AD.

8. The transgenic non-human animal of claim 7, wherein the transgenic nucleotide sequence encoding carboxyl-terminal truncated apoE is overexpressed, resulting in elevated levels of carboxyl-terminal truncated apoE relative to an animal of the same species not harboring said transgene.

9. The transgenic non-human animal of claim 7, wherein the apoE is apoE4.

10. The transgenic non-human animal of claim 9, wherein said carboxyl-terminal truncated apoE4 is apoE4(Δ272-299).

11. The transgenic non-human animal of claim 7, wherein the symptom of AD is the presence of neurofibrillary tangles in a neuronal cell.

12. A method of screening for biologically active agents that modulate a phenomenon associated with Alzheimer's disease (AD), comprising:

(a) contacting a cell that produces a carboxyl-terminal truncated apoE with a test agent; and

(b) determining the effect of said agent on the level of carboxyl-terminal apoE in the cell.

13. The method of claim 12, wherein the cell is a cell in a non-human transgenic animal that comprises, as a transgene, a nucleic acid that comprises a nucleotide sequence encoding apoE, and wherein a reduction in the level of carboxyl-terminal truncated apoE results in a reduction in neurofibrillary tangles.

14. The method of claim 12, wherein the cell is an *in vitro* cell.

15. A method of screening for biologically active agents that reduce a proteolytic activity of an enzyme that catalyzes the proteolytic degradation of apoE in a neuronal cell, comprising:

contacting the enzyme with a test agent and a substrate that provides a detectable product when acted on by the enzyme; and

determining the effect, if any, of the test agent on formation of detectable product.

16. The method of claim 15, wherein the substrate is a peptide of the formula $(P_3)_nP_2P_1$-X, wherein $P_4P_3P_2P_1$ is a peptide, wherein X is a moiety that is linked to the carboxyl terminus of the peptide, and that provides a detectable signal when cleaved from the peptide upon action by the enzyme, P_1 is a hydrophobic residue selected from the group consisting of leucine, phenylalanine and methionine; P_2 is proline; P_3 is alanine, and $n \geq 2$.

17. An isolated cell comprising a nucleic acid molecule that comprises a nucleotide sequence that encodes a carboxyl-terminal truncated form of apoE.

18. The isolated cell of claim 17, wherein the apoE is apoE4.

19. The isolated cell of claim 17, wherein said carboxyl-terminal truncated form of apoE4 is apoE4(Δ272-299).

20. The isolated cell of claim 17, wherein said cell is a neuronal cell.

21. A method of inhibiting formation of neurofibrillary tangles in an individual, the method comprising: inhibiting interaction of a carboxyl-terminal truncated form of apoE with other components of a neurofibrillary tangle.

22. The method of claim 21, wherein the other components of a neurofibrillary tangle are selected from the group consisting of phosphorylated tau and phosphorylated NF-H.

23. A method of inhibiting formation of neurofibrillary tangles in a neuronal cell of an individual, the method comprising: contacting the neuronal cell with an agent that inhibits an enzymatic activity of an enzyme in the neuronal cell that catalyzes cleavage of apoE in the cell to generate carboxyl-terminal truncated apoE.

24. The method of claim 23, wherein the agent is a peptide selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO:1), Ala-Ala-Pro-Leu (SEQ ID NO:3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO:4).

25. A pharmaceutical preparation comprising:

a) an inhibitor of a chymotrypsin-like protease inhibitor;

b) an agent selected from the group consisting of an acetylcholinesterase inhibitor, a non-steroidal anti-inflammatory agent, a cyclooxygenase-2 inhibitor, and a monoamine oxidase inhibitor; and

c) a pharmaceutically acceptable excipient.

26. A method of treating Alzheimer's disease, the method comprising:

a) assaying for the presence of carboxyl-terminal truncated apoE in a neuronal cell; and

b) administering an inhibitor of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell.

27. A kit comprising:

a composition comprising an inhibitor of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell; and a pharmaceutically acceptable excipient; and

instructions for administering the composition to an individual in need of thereof.

28. A method of treating Alzheimer's disease, the method comprising:

administering an inhibitor of a chymotrypsin-like serine protease in an amount effective to inhibit an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell, wherein the enzyme is inhibited and the level of neurofibrillary tangles in a neuronal cell in the individual is reduced.

29. A composition comprising:

a) an agent that inhibits an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell; and

b) a pharmaceutically acceptable excipient.

30. The composition according to claim 29, wherein the agent is selected from the group consisting of Ala-Ala-Pro-Phe (SEQ ID NO:1), Ala-Ala-Pro-Met (SEQ ID NO:2), Ala-Ala-Pro-Leu (SEQ ID NO:3), and Ala-Ala-Ala-Ala-Pro-Phe (SEQ ID NO:4).

31. A method of reducing the level of carboxyl-terminal truncated apoE in a neuronal cell, the method comprising:

contacting the cell with an agent that reduces activation of an enzyme that catalyzes the formation of carboxyl-terminal truncated apoE in a neuronal cell by $A\beta_{1-42}$, wherein a reduction in the activation of the enzyme results in a reduction in the level of carboxyl-terminal truncated apoE in the cell.